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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/871,809	KEREM, BATSHEVA	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-6 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-8 are pending.

Applicants' amendment filed June 16, 2005 is acknowledged. Applicants' response has been fully considered. Claims 1, 3-6 and 8 have been amended.

Newly amended claim 1, in part, directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 1, in part, recites a method of treating cystic fibrosis comprising expressing in cells, tissue or organs of an individual in need thereof an effective amount of an alternative splicing factor (ASF) capable of at least partially correcting aberrant splicing of a transcript of a CFTR gene, which is distinct from the original claim 1, directed to a method of treating of an individual suffering from a disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, the method comprising: administering to said cells of the individual or to tissue or organs of said individual comprising said cells, an effective amount of an alternative splicing factor (ASF).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 1, the part of expressing in cells, tissue or organs of an individual in need thereof an effective amount of an ASF in the method of treating cystic fibrosis, is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Therefore, claims 1, 3-6 and 8, directed to method of treating cystic fibrosis comprising administering to cells, tissue or organs of an individual in need thereof an effective amount of an alternative splicing factor (ASF) are examined.

Withdrawn Claim Rejections - 35 USC § 112

2. The previous rejection of claims 2 and 7, under 35 U.S.C. 112, first and second paragraphs, is withdrawn in view of applicants' cancellation of the claim in the amendment filed June 16, 2005.

New Claim Objection

3. Claim 1 is objected to because of the use of the term "CTFR", where fully spelled out words should be indicated in the first occurrence. See also claim 5 for "SR protein".

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Previous rejection of claims 1, 3-6 and 8 under 35 U.S.C. 112, first paragraph is maintained. Applicant's arguments have been fully considered, and the response to the argument is shown below.

Claims 1, 3-6 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cell lines established from samples of cystic fibrosis (CF) patient resulting from an abnormal expression of genes caused by aberrant splicing in cells, comprising transfecting the cells with expression vector to produce a specific alternative splicing factor (ASF) such as hnRNP A1 or E4-ORF6, whereby the abnormal expression shifts towards normal expression of the gene, does not reasonably provide enablement for a method of treating cystic fibrosis comprising administering to cells or tissue or organs of an individual in need thereof an effective amount of an ASF capable of at least

partially correcting aberrant splicing of a transcript of a CTFR gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 3-6 and 8 are directed to a method for treating cystic fibrosis comprising administering to cells or tissue or organs of an individual in need thereof an effective amount of an ASF capable of at least partially correcting aberrant splicing of a transcript of a CTFR gene. The specification, however, only discloses cursory conclusions without data supporting the findings, which states that the method of invention concerns administering to the cells or to tissue or organs of the individual comprising the cells, an alternative splicing factor (ASF), e.g., any factor which is known to modulate alternative splicing, for example, members of the SR protein family including SF2/ASF, the heterogeneous ribonucleoprotein A1 (hnRNP A1), or the agonist of the naturally occurring ASFs, and the administration of the ASFs to the cells causes a shift in the expression of the gene responsible for genetic disease towards normal expression (pages 4-6). There are no indicia that the present application enables the full scope in view of a method for treating cystic fibrosis using an ASF as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the ASFs including various naturally occurring ASFs and their agonists, and the treating conditions of ASF such as effective amount used in the treatment of CF, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for the examples of certain cellular and viral splicing factors such as hnRNP A1 or E4-ORF6 that modulate the splicing pattern in epithelial cell line established from the sample of CF patient (Example 5, pages 14-17).

(3). The state of the prior art and relative skill of those in the art:

The related arts, e.g., Mayeda *et al.* (Mol. Cell. Biology 13, 2993-3001 (1993)) teach the essential splicing factor SF2/ASF and hnRNP A1 modulate alternative splicing *in vitro* of pre-mRNAs. An excess of SF2/ASF prevents inappropriate exon skipping in natural β-tropomyosin pre-mRNA, while an excess of hnRNP A1 does not cause inappropriate exon skipping in natural pre-mRNA; and Nordqvist *et al.* (Mol. Cell. Biology 14, 437-445 (1994)) teach the adenovirus early region 4 proteins E4 open reading frame (E4-ORF3) and E4-ORF6 regulate major late mRNA accumulation by stimulating constitutive splicing. E4-ORF3 facilitates exon inclusion while E4-ORF6 facilitates exon skipping. However, the related art does not teach the treatment of CF using various ASFs, and the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on

identities of the ASF administered, and the treating conditions for administering ASF, to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method for treating cystic fibrosis comprising administering to cells or tissue or organs of an individual in need thereof an effective amount of an ASF. As indicated in the related art (Mayeda *et al.*, Mol. Cell. Biology 13, 2993-3001 (1993)), hnRNP A1 can promote alternative exon skipping, however this effect is not universal and is dependent on the size of the internal alternative exon and on the strength of the polypyrimidine tract in the preceding of intron. The specification (e.g., Example 3, Table 2) also indicates transfection of p5T generated two splicing products: 24% of transcripts were aberrantly spliced (330 bp) and the rest (76%) were correctly spliced (513 bp), and transfection of p9T only generated 3% of transcripts being aberrantly spliced; however, transient cotransfection of p5T and pCG-A1 into COS-1 resulted in a substantial increase in aberrantly spliced transcripts (44%) and transient cotransfection of p9T and pCG-A1 does not affect the p9T minigene pattern. Thus, the invention is highly unpredictable regarding the outcome of the treatment without identifying the abnormal gene and the ASF administered.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for treating cystic fibrosis comprising administering to cells or tissue or organs of an individual in need thereof an effective amount of an ASF. The specification indicates the effect of overexpression of the cellular hnRNP A1 on the splicing of 3849+10 kb C->T or polyT minigenes, or the effect of overexpression of the viral E4-ORF6 on

the splicing of 3849+10 kb C->T minigenes (Examples 2-5; Figs.3-7), where the mutation (3849+10 kb C to T) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene has been linked to CF patients with abnormal epithelial function. However, the specification has not demonstrated the in vivo treatment of CF, nor has indicated how to extrapolate the in vitro or ex vivo data to in vivo treatment, and there are no working examples indicating the effect of a known ASF in the treatment of the CF. Furthermore, the specification has not indicated the use of any agonist of a naturally occurring ASF, nor has demonstrated the administration of the protein product of ASF to cells is effective in shifting abnormal expression of the gene to normal expression and in the treatment of CF. Moreover, there are no working examples indicating treating conditions such as effective amount of the ASF protein product for treating CF in vivo. As indicated in the art (see the section of unpredictability), ASF such as hnRNP A1 can promote alternative exon skipping, however this effect is not universal. Since the specification fails to provide sufficient guidance on treating CF using an identified AFP, it is necessary to carry out undue experimentation to identify an effective ASF and to assess the effect of the ASF in treating CF.

(6). Nature of the Invention

The scope of the claims encompass treating cystic fibrosis comprising administering to cells or tissue or organs of an individual in need thereof an effective amount of an ASF, but the specification has not demonstrated the treatment of CF with an effective AFP in vivo. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed method, the effect of ASF and the outcome of treatment are unpredictable, and the

teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out undue experimentation to identify an effective ASF and to assess the effect of the ASF in CF resulting from aberrant splicing of a CTFR gene.

5. Previous rejection of claims 1, 3-6 and 8 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is maintained. Applicant's arguments have been fully considered, and the response to the argument is shown below.

Claims 1, 3-6 and 8 are directed to a method for treating cystic fibrosis comprising administering to cells or tissue or organs of an individual in need thereof an effective amount of an ASF capable of at least partially correcting aberrant splicing of a transcript of a CTFR gene, thereby treating CF in the individual. While the specification indicates that ASF may be administered to the cells by inserting a nucleotide sequence expressing the ASF in an expression vector, and the cells of the individual are transfected with the expression vector to produce ASF, or by attaching the expression vector to targeting moiety, e.g., antibody or a ligand of a specific receptor which can specifically bind to the membranes of the desired cells, and the expression vector being administered systemically, or by administering an ASF as the protein product itself (page 5, line 26-page 6, line 25), the specification does not disclose a genus of variants for ASF used in the treatment of CF in vivo.

The specification demonstrates the in vitro or ex vivo effect of administering a specific ASF to the cell lines, e.g., the effect of overexpression of the cellular hnRNP A1 on the splicing of 3849+10 kb C->T or polyT minigenes, or the effect of overexpression of the viral E4-ORF6

on the splicing of 3849+10 kb C->T minigenes (Examples 2-5; Figs.3-7), however, it has not demonstrated the effect of an identified ASFs in correcting aberrant splicing of a transcript of CTFR gene and in the treatment of CF in vivo. Furthermore, there are no in vivo working examples indicating the use of an effective amount of an identified ASF in treating CF. The lack of description of the use of an effective ASF in the treatment of CF in vivo, and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Response to Arguments

Applicants indicate clams 1, 3-6 and 8 have been amended to limit the subject matter to the treatment of cystic fibrosis. Applicants have provided evidence that the underlying genetic pathology of cystic fibrosis can be corrected using ASF by demonstrating that correction of aberrant splicing of CFTR transcripts in cells of cystic fibrosis patients by expression of recombinant exogenous splicing factors (Example 5). CF is a severe autosomal recessive disease caused by well characterized mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, as indicated in the specification, aberrant splicing resulting from such mutations can be at least partially corrected by ASFs. With respect to the experimental data the present case presents a simple one gene – one effect relationship in which mutation of a known and quantifiable gene lead to a well characterized effect. In such case, strong correlation between in-vitro data and in vivo results is expected, for example, Anderson *et al.* (Biochem. Biophys. Res. Commun. 2003, 310(2):627-633) indicates regulation of an ASF (namely hnRNP) promotes production of a functional gene product and led researchers to conclude that such

regulation offers a "therapeutic modality for individuals with familial dysautonomia (FD)"; Regarding treating conditions, although the specification does not provide the exact amount of an ASF for treatment, such therapeutically effective amount can be easily determined in light of the teachings in the specification, and the specification also teaches the administration of ASF (pages 6, lines 6-16). Thus, the in vitro results and detailed description clearly provide the enablement and written description support necessary for making and using the present invention without having to resort to trial and error experimentation (pages 4-7 of the response).

Applicants' response has been fully considered, however, the argument is not found persuasive because the specification does not demonstrate the use of an effective ASF in the treatment of CF resulting from aberrant splicing of a transcript of CTFR gene, and there are no working examples indicating the amount of a specific ASF is effective in the treatment of CF. Examples in specification merely demonstrate certain cellular and viral splicing factors such as hnRNP A1 or E4-ORF6 that modulate the splicing pattern in epithelial cell line established from the sample of CF patient (Example 5), it does not demonstrate the correlation of in vitro data with the in vivo treatment. The post filing reference of Anderson *et al.* merely suggests that the possible use of EGCG as a therapeutic modality for patient with FD, it still requires undue experimentation to determine an effective amount of the EGCG in treating FD. Since the specification does not describe the correlation of in vitro data with in vivo treatment, and there is no description in the use of an effective amount of an identified ASF in the correcting aberrant splicing of a CTFR gene and in the treatment of CF in vivo, further undue experimentation is required to identify an effective ASF in the treatment of CF in vivo. Therefore, without undue

experimentation, one skilled in the art does not know how to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 3-6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3-6 and 8 are indefinite because of the use of the term "at least partially correcting aberrant splicing of a transcript of a CTFR gene", it is not clear to what extent the aberrant splicing of the transcript of CTFR gene is corrected (e.g., 30%, 50% or 90%), and what effect the administration of an effective amount of ASF would produce. Claims 3-6 and 8 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

Response to Arguments

Applicants indicate claim 1 has been amended to include "thereby treating cystic fibrosis in said individual" with respect to the effect of ASF in the treatment (page 7 of the response).

Applicants' response has been considered, however, the argument is not found persuasive because the term "treating cystic fibrosis" does not reflect the effect of ASF in treating cystic fibrosis.

Conclusion

7. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D. CMK
Patent Examiner

CMK
August 10, 2005

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER